

REMARKS

Applicant acknowledges receipt of a Non-Final Office Action (“the Action”), dated October 11, 2006. Applicant presently amends claims 1-3, 5, 7, 8, 10, 11 and 14. Claims 15-21 are added and claim 9 is canceled. Upon entry of these changes, claims 1-8 and 10-21 will be pending in this application.

No new matter has been introduced. Support for the claim amendments can be found in the specification, e.g., in the paragraphs cited below from the published version, US 2005/0075361:

- Claim 1 – paragraph [0073];
- Claim 5 – paragraphs [0065] to [0068] and [0073];
- Claims 8 and 10 – paragraph [0068];
- Claim 11 – paragraph [0066] and Table 1;
- Claims 15 and 16 – paragraph [0074];
- Claims 17 and 18 – paragraph [0068];
- Claim 19 – paragraphs [0066] and [0068] and Table 1;
- Claim 20 – paragraphs [0070] and [0076] and original claim 12; and
- Claim 21 – paragraph [0104].

The revisions to claim 14 introduce recitations from base claim 5, thereby placing claim 14 in independent form. The amendments to claims 2 and 3 comport with changes to claim 1. Finally, the changes to claim 7 place this claim in a more appropriate dependent form.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the following remarks.

Claim Rejection under 35 U.S.C. § 112

Claims 1-14 were rejected for allegedly “failing to comply with the written description requirement” (Action, page 8). The PTO asserted that “[i]t is unclear from the claims what is encompassed” by “a generic recitation of ‘R’” and “aliphatic” (*id.*), and that the “generic language” in the claims “could encompass myriad of compounds” (page 9).

Thus, the examiner is heard to reject the subject claims more for concerns over clarity (definiteness) than written description. If Applicant has misunderstood the situation, then Examiner Desai's elaboration is requested.

Applicant believes that the original claims are not indefinite or otherwise out of compliance with Section 112. Nonetheless, to expedite prosecution Applicant has revised the claims, as indicated above, in a good-faith effort to address the examiner's stated concerns. Certainly, a skilled person would comprehend, from the present claims, the metes and bounds of Applicant's invention. Applicant therefore requests withdrawal of the apparent rejection of claims 1-14 for indefiniteness.

Claim rejection under 35 U.S.C. § 103(a) for obviousness

On pages 4-7 of the Action, the claims were rejected over a series of references. The cited references are Buchwald *et al.*, *J. Med. Chem.*, 42: 5160-68 (1999); Stinchcomb I, *Pharm. Res.*, 13(10): 1519-1523 (1996); Stinchcomb II, *Pharm. Res.*, 12(10): 1526-29 (1995); Hu *et al.*, U.S. Pat. 5,750,534; Hu *et al.*, U.S. Pat. 6,225,321; Hu *et al.*, EP 1149836; and Li-Heng Pao *et al.*, *J. Chromatography B*, 746: 241-47 (2000).

The PTO alleged that:

- (1) Stinchcomb I "teaches that buprenorphine is a well known analgesic" (Action, page 5);
- (2) Hu '321 and Pao teach dinalbuphine diesters (page 6);
- (3) "Nalbuphine is also an analgesic and acts on the same receptor" as buprenorphine (*id.*);
- (4) Hu '836 teaches "polynalbuphine" (*id.*);
- (5) Hu '534 teaches buprenorphine (*id.*); and
- (6) Buchwald and Stinchcomb teach buprenorphine monoesters that are "alkyl homologs of the claimed compounds" (*id.*).

Regarding assertion (6), the PTO acknowledged that the claims "proviso out the prior art compounds" but asserted that "[s]tructurally similar compounds possess similar properties" (Action, page 6).

1. The law on obviousness

A *prima facie* case of obviousness has three requirements. First, a single prior art reference or a combination of references must teach or suggest each and every feature of the claimed invention. *In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974). Second, there must be some reason, motivation, or suggestion to modify the single reference or combine the references in order to make the claimed invention. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Third, the prior art must provide “a reasonable expectation of success” that modifying the single reference or combining the references would result in the claimed invention. *Id.* If any one of these three requirements is not met, a rejection for obviousness cannot stand.

Even if a *prima facie* case of obviousness is established, it may be overcome by secondary considerations (i.e., objective evidence of nonobviousness). “Objective evidence or secondary considerations such as unexpected results,...long-felt need, failure of others,...and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are...submitted.” MPEP § 2141 III.

2. The cited references teach away from the claimed monoesters

In relation to the claimed buprenorphine monoesters, the PTO has not demonstrated that the skilled artisan would have been motivated to make the claimed buprenorphine monoesters or to use them for analgesia. Indeed, the failure of the cited references to address or even to consider buprenorphine monoesters, in the context of improving transdermal buprenorphine delivery, effectively led the person of ordinary skill away from such development.

For instance, Stinchcomb I and II failed to improve the flux of buprenorphine across a lipid membrane by using C₃ alkyl monoesters of buprenorphine. Stinchcomb I reported instead that “in no instance did the buprenorphine flux through skin from a prodrug solution exceed the flux of buprenorphine base itself in vitro” (summary of *Results*, page 1519).

Accordingly, Stinchcomb I taught away from the potential use of a buprenorphine monoester as a transdermal drug. In fact, Stinchcomb I stifled the investigation of buprenorphine monoesters as drugs for any other therapeutic uses, e.g., as long-acting analgesics. Not surprisingly, Applicant is unaware of any subsequent mention, in the

academic or patent literature, implicating non-C₃ alkyl buprenorphine monoesters for pain management.

In much the same vein, consider the teaching in both Stinchcomb I and Imoto *et al.*, *Biol. Pharm. Bull.*, 19(2): 263-67 (1996), that buprenorphine monoesters with a longer aliphatic chain exhibited a worse transdermal character than buprenorphine acetate. Again, the prior art counseled the skilled artisan away from such buprenorphine monoesters.

Buchwald concerns the development of a model that is used to estimate the approximate rate of hydrolysis of a prodrug or soft drug candidate. Three C₃ alkyl buprenorphine monoesters disclosed in Stinchcomb I were tested in Buchwald. Accordingly, Buchwald provides no additional information that would have motivated the skilled artisan to pursue, in an analgesic context, any buprenorphine monoesters as presently claimed.

3. The claimed buprenorphine monoesters and diesters differ substantially, in structure and in analgesic properties, from prior-art nalbuphine monoesters and diesters

The PTO is heard to acknowledge that all of the cited references are silent with respect to the synthesis of dibuprenorphine diesters. With this understanding, the PTO nevertheless has reasoned that the claimed dibuprenorphine diesters are obvious over dinalbuphine diesters in the prior art because (1) Hu '321 and Pao teach dinalbuphine diesters, (2) "Nalbuphine is [] an analgesic and acts on the same receptor" as buprenorphine, and (3) "[s]tructurally similar compounds possess similar properties" (Action at page 6).

The PTO's rationale is contradicted, however, by the fact that buprenorphine and nalbuphine significantly differ in chemical structure, mechanism of action, and analgesic properties.

First, buprenorphine and nalbuphine differ from each other in relation to at least seven structural features:

- (1) buprenorphine has a methoxy group, while nalbuphine has a free hydroxyl group (on the cyclohexenyl ring);
- (2) the methoxy group in buprenorphine is directed upward, whereas the hydroxyl group in nalbuphine is directed downward;

- (3) the methoxy group in buprenorphine is attached to a bridged carbon center, unlike the hydroxyl group in nalbuphine;
- (4) the cyclohexenyl ring of nalbuphine containing the hydroxyl group has a double bond, unlike the cyclohexyl ring of buprenorphine containing the methoxy group;
- (5) buprenorphine has a 2-hydroxy-3,3-dimethylbutyl group, while nalbuphine has no substitution at the corresponding position;
- (6) nalbuphine has a tertiary hydroxyl group at a fused carbon center, unlike buprenorphine; and;
- (7) buprenorphine contains a methylcyclopropyl group on the nitrogen atom, while nalbuphine has a methylcyclobutyl group on the nitrogen atom.

In view of these differences, it is not reasonable for the PTO to assert, in rationalizing the pending obviousness rejection, that buprenorphine and nalbuphine are structurally similar.

Second, buprenorphine and nalbuphine are distinct from each other in terms of mechanism of action. That is, buprenorphine exerts its analgesic effect by binding to the opioid μ receptor as a μ -receptor partial **agonist**, and it is an **antagonist** to the opioid κ receptor. In sharp contrast, nalbuphine exerts its analgesic effect by binding to the opioid κ receptor as a κ -receptor **agonist**, and it is an **antagonist** to the opioid μ receptor. Contrary to the PTO's assertion, therefore, buprenorphine and nalbuphine do not display the same activity on the same receptor.

These significant differences in chemical structure and mechanism of action carry through to significant differences in analgesic properties, separating buprenorphine and nalbuphine. For example, buprenorphine is a **potent** analgesic, whereas nalbuphine is a **moderate** analgesic. Also, when buprenorphine is co-administered with an opioid-like compound (e.g., morphine), the analgesic effect is **increased**. By contrast, when nalbuphine is co-administered with an opioid-like compound, the analgesic effect is **decreased**. See Hartree, *Palliative Medicine*, 19: 168 (2005) (copy appended).

It is apparent from the foregoing that none of the elements of the PTO's stated rationale bears up under factual examination. The very differences that separate buprenorphine from nalbuphine bespeak a separation, between their respective monoesters

and diesters, that the prior art does not bridge. For this reason alone, withdrawal of the pending obviousness rejection is warranted.

4. The long-acting analgesia achieved with Applicant's claimed invention would have been unexpected in view of the art of record

As noted above, the prior art of record gives no indication whatever that the person of ordinary skill would have expected the result of long-acting analgesia by any particular means, let alone via a buprenorphine-based pharmacology. Thus, Applicant's achievement of this end, by way of the presently claimed invention, would have been wholly surprising to the skilled artisan, a fact that further vindicates the patentability of the present claims.

In this regard, Applicant would direct attention to his disclosure of a prolongation of buprenorphine analgesic action, achieved with the claimed invention. Thus, the present application evidences a lengthened duration of analgesic action for buprenorphine base, which the skilled artisan would not have expected. See Pharmacological Example 2, Table 3, and Figures 20-A and 20-B of the application. Likewise, employing buprenorphine monoesters (Pharmacological Examples 3 and 4, Table 3, and Figures 21-A to 21-E and Figure 22) and dibuprenorphine diesters (Pharmacological Example 5, Table 3, and Figures 23-A and 23-B) in accordance with the claimed invention effected a surprising extension in the duration of analgesic action. None of the cited references, including Hu '534 and Hu '321, presages such results.

In view of the foregoing remarks, Applicant submits that the claimed invention is non-obvious over the cited prior-art teachings. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 1-14 under Section 103.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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Letters to the editor

NSAIDs: gastroprotection or selective COX-2 inhibitors?

Sir – I read with interest the article by Andrew Dickman and John Ellershaw entitled ‘NSAIDs: gastroprotection or selective COX-2 inhibitors’, published in *Palliative Medicine* 2004; 18: 276–86. I would like to make a couple of comments, particularly in relation to the guidelines at the end of the article.

Guidelines are based upon efficacy and risk. The choices within a guideline are based upon increased efficacy, reduced risk (toxicity) or reduced costs with equivalent efficacy and risk. Guidelines can be directed by evidence in which there may be large ‘holes’ which are filled in by expert opinion due to lack of evidence-based studies, or guidelines may be clinically based with expert opinion of choices directing therapy based upon practicalities, or guidelines may be regional due to drug availability.

The article by Dickman and Ellershaw is a nice synopsis of the use of NSAIDs in rheumatic disease with a discussion centred upon gastrointestinal toxicity. There is little attention given to the renal toxicity (greater or equal with COX-2 inhibitors compared to nonselective COX inhibitors) and cardiovascular toxicity (the reasons for rofecoxib’s withdrawal from the market). Both toxicities have received a great deal of attention in the literature.^{2–8}

I find it extraordinary that a palliative care guideline was included in this review where 1) the efficacy of COX-2 inhibitors in advanced cancer was not discussed (for which there is no data or little data)⁹ and 2) there is minimal discussion about the renal and cardiovascular toxicity within the text and hence recommendations were slanted towards one toxicity. Guidelines based solely upon gastrointestinal toxicity in noncancer patients are unlike any other recommendation for palliative patients conceived, to my knowledge.

The guideline is out of context with the body of the article as it solely deals with NSAIDs, gastrointestinal toxicity and rheumatic disease. It takes an article of faith that COX-2 inhibitors are equivalent to COX nonselective agents, for which there is no evidence (as there is evidence in rheumatic disease).⁹

The equivalent recommendation is to suggest that antibiotic choices for pulmonary infections are guidelines that fit antibiotic choices for gastrointestinal infections.

In the same issue Dr Lunder and colleagues¹⁰ stated: ‘Evidence about the effect of clinical guidelines on

practice shows serious deficiencies partly due to the quality of guidelines.’ The present published guidelines by Mr Andrew Dickman and Dr John Ellershaw are null and void within the month of publication. Evidence-based guidelines take time to develop and require a broader view of pharmaceutical management that includes efficacy within the context of the disease to be managed, all drug toxicities and interactions, as well as cost.

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A reply to Dr Davis and other correspondents

Sir – We thank Dr Human,¹ Dr Shah and Ms Thomas,² and Dr Davis for their comments on our paper.³ Clinical practice guidelines should be systematically developed statements which assist practitioner and patient decisions.⁴ It is important to note that guidelines are not treatment protocols and the prescriber retains freedom of choice. Nonetheless, guidelines are developed to enhance the appropriateness of treatment, improve the quality of patient care and ensure the cost effectiveness of treatment. The methods of developing guidelines follow recognized steps, which include the review of scientific evidence, together with expert opinion.⁵ More often than not, the clinical scope of level 1 evidence is so narrow that useful guidelines cannot be developed from such sources alone; recommendations therefore require further input from other evidential sources, such as expert or consensus opinion. Guideline development incorporates not solely the academic, but also processes of judicious extrapolation, interpretation and value judgement.⁶ The development and introduction of guidelines are appropriate in situations of uncertainty and where there exists reliable scientific evidence which can form the basis for the development of guidelines.

Dr Davis suggests that the clinical practice guideline included in our paper was not fit for the purpose, stating that there is little or no data for the use of these drugs in cancer patients. The benefit of hindsight is a wonderful thing, given the recent withdrawal of rofecoxib and the furore that now surrounds NSAIDs and COX-2 inhibitors. Nonetheless, the guideline was conceived because NSAIDs and COX-2 inhibitors continue to be used in palliative care despite the lack of clear scientific evidence. We believed it necessary to develop a guideline, using the best available scientific evidence and expert opinion at the time. The paper clearly pointed out that experience in palliative care patients is limited and the gastrointestinal guideline was based upon known risk factors which equally apply to the palliative care population; it is unlikely that a terminal illness confers a reduced potential for NSAID-induced damage. These risk factors were obtained from a variety of sources as discussed in our paper; female sex was not identified as a risk factor in any of them. Dr Shah and Ms Thomas raise important points; their work identified female sex as a risk factor in the palliative care population. This warrants further investigation. They also correctly mention that coprescription of an SSRI may become an important risk factor.

With respect to the renal effects, we agree with Dr Davis that the paper did not fully discuss these. Nonetheless, we believe the paper provided enough content for the reader to understand that all NSAIDs and COX-2 inhibitors have a similar deleterious effect on renal

function. Hence, the guideline presented in our paper would be unaffected by NSAID and COX-2 inhibitor renal effects, reflecting the lack of lengthy discussion.

Cardiovascular (CV) effects of the NSAIDs and COX-2 inhibitors are still controversial and the withdrawal of rofecoxib as a result of evidence from the APPROVe⁷ trial is unfortunate. APPROVe was a multicentre, randomized, placebo-controlled, double-blinded clinical trial to determine the effect of three years of treatment with rofecoxib 25 mg on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenomas. Although an absolute CV event risk rate has been determined from this trial, it is important to note that APPROVe was not designed to specifically examine the CV safety profile of rofecoxib. The problem with analysing data from a trial for a condition that it was not specifically designed for can produce errors in interpretation. It will be interesting to review the results when published in order to place the risks, or benefits, into perspective, particularly as the theory suggested a benefit with respect to the trial objectives.

The pharmacology of the COX-2 inhibitors would suggest that there is likely to be an impact on the CV system,³ but the actual clinical impact of all NSAIDs (except aspirin) is still uncertain, a fact highlighted by the finding in a recent Alzheimer's prevention trial (see below). An important consideration is the appropriate use of low-dose aspirin. In patients at risk of a CV event, low-dose aspirin is likely to be prescribed. Coprescription of a conventional NSAID in this situation not only increases the risk of a GI event,⁸ but may also reduce the beneficial antiplatelet effect of aspirin.⁹ Coprescription of a COX-2 inhibitor does not interfere with aspirin's antiplatelet effect; the impact on GI toxicity is unclear, but it is believed to increase the risk of toxicity to that of a conventional NSAID.¹⁰

In the past few days, information has come to light that complicates the matter further. The Medicines and Healthcare Products Regulatory Agency (UK) have issued interim guidance in lieu of a recent trial involving celecoxib: 'Patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (i.e. conventional NSAID) treatments as soon as is convenient.'¹¹ This is itself an interesting statement because the CV safety of NSAIDs is unclear. This is highlighted by a further clinical trial in America, involving celecoxib, which has just been halted. This trial compared celecoxib to placebo or naproxen in Alzheimer's disease prevention. The information that is in the public domain at the time of writing states that naproxen caused 50% more CV events than placebo; celecoxib was not associated with an increased risk.¹²

Treatment with these drugs will invariably be individualized, dependent upon coexistent risk factors. There

are gaps in our current knowledge; we need to know if the perceived GI benefit of a COX-2 inhibitor + aspirin \pm a proton pump inhibitor (PPI) outweighs the risk of a CV event from this combination, or indeed the GI risk associated with a NSAID + PPI + aspirin. In addition, we also need to further understand the CV implications of NSAID + aspirin + PPI. Until such evidence is available, we have to rely upon judicious extrapolation, interpretation and value judgement. As a final thought: 'Medical practitioners should regard the recommendations of consensus development conferences as useful reference tools; not the rulings of philosopher kings, but the attempt of thoughtful people to share their knowledge – albeit imperfect – with other people.'¹³

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Autopsy in palliative medicine

Sir – I read with interest the paper 'A case for autopsy in palliative medicine?' (Volume 18, number 7, October 2004) and congratulate the authors on looking at something, for some reason, seldom discussed in palliative medicine circles. When, as they remind us, the number of autopsies is falling steadily (and has always been very few in palliative medicine units), anything that can be done to encourage autopsies with least upset or anxiety for the relatives is important.

I should like to learn from colleagues around the world in hospital palliative care teams, and palliative care units within general hospitals whether they request autopsies, what difficulties they encounter, what they have learnt about previously inexplicable symptoms.

The time between death and autopsy, or between death and funeral, varies from place to place but it is obviously important that the funeral should be delayed as little as possible for the sake of the grieving, but so co-operative, relatives. Having an agreed arrangement with the pathologists as well as with the undertakers will presumably facilitate this.

The authors imply that, ready as the relatives were to permit an autopsy, there was discontent amongst some of the professional carers. May we know more? What was the cause of it? How big is the 'team' which needs to be involved in the decision to request the autopsy? Should it always involve the family doctor and/or community nurses, or if the relatives have any religious affiliation, should it involve the clergy? After all, they may long continue to be involved in supporting the relatives. Should it involve the teams previously involved in the care – physicians, surgeons, oncologists?

Sadly I must disagree with their assertion that palliative care is "... about protecting vulnerable, incurably ill patients from over-zealous doctors and their unnecessary investigations." I hope it is more than that! We are not clinical policemen or ethics guardians. We are enablers and demonstrators, sometimes teachers and tutors – at every opportunity enabling colleagues to care as, I suspect, they would like to and demonstrating to them

how, employing the principles of palliative medicine, they might do so.

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Caution with nalbuphine in patients on long-term opioids

Sir – We have recent experience of two patients on regular mu agonist opioid analgesics who experienced increased pain and opioid withdrawal symptoms when given nalbuphine (Nubain) for breakthrough pain.

Nalbuphine is a semi-synthetic opioid closely related structurally to naloxone. Its indications include moderate to severe pain, perioperative analgesia and myocardial infarction. It achieves its analgesic effect via kappa opioid receptor agonism.

It is however a mu receptor antagonist. It can be an effective analgesic for acute pain but may cause problems if given to patients already taking mu agonist opioids for continuing pain.

Several authors suggest caution in the use of nalbuphine for patients already taking other opioids.^{1–3}

A recent *BMJ* Lesson of the Week describes a similar case and highlights a further concern, the potential of nalbuphine to increase requirements of opioid analgesics after arrival at hospital.⁴

Nalbuphine is not well known to palliative care physicians and receives only brief mention in the Palliative Care Formulary under a section headed 'opioid antagonists'.⁵

Several factors may result in nalbuphine appearing to be an attractive alternative to diamorphine in the community. Nalbuphine has low abuse potential and is not a controlled drug. The BNF gives a positive impression without referring to its potential problems.⁶ Similarly, the data sheet for nalbuphine makes no mention of its potential to antagonize analgesia or precipitate opioid withdrawal symptoms.

We believe that there should be heightened awareness of the potential problems of using nalbuphine in patients already taking other opioids. Part of the solution lies in ensuring that patients on long-term opioids have adequate supplies of appropriate breakthrough analgesics at home.

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Case A

A 54-year-old man with painful pelvic recurrence of carcinoma of rectum was pain controlled with methadone 10 mg twice daily after morphine and oxycodone had given poor results. An on-call GP gave nalbuphine 10 mg IM for breakthrough pain which resulted in increased pain and symptoms of restlessness and agitation. He was admitted to the hospice tachycardic, sweaty and restless. He required subcutaneous diamorphine 20 mg and midazolam 10 mg on two occasions within two hours to achieve symptom control.

Case B

A 49-year-old man with carcinoma of prostate and painful spinal metastases was controlled on morphine SR 360 mg twice daily. He was seen at home by an on-call GP because of increased pain and was given nalbuphine 10 mg IM. Within five minutes, the patient experienced increased pain and symptoms of opioid withdrawal. However, the attending doctor sent the patient to hospital suspecting an anaphylactic reaction.

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Prescribing palliative oxygen: a clinician survey of expected benefit and patterns of use

Sir

Background: Current guidelines for funding domiciliary oxygen are derived from data in people with chronic

obstructive pulmonary disease where benefit is measured in terms of improved survival.¹ Such data cannot be generalized to the palliative care population. In people with life-limiting illness, demonstrable benefit must include either decreased (subjective) breathlessness or an improved ability to conduct activities of daily living.

Palliative oxygen is frequently prescribed as one aspect of the management of intractable breathlessness in people who are either normoxaemic or mildly hypoxaemic ($\text{PaO}_2 > 55$ mmHg). In the setting of palliative care, oxygen is often offered as a therapeutic trial with poorly defined end-points for its continuation. A number of small studies of short duration have been carried out in people at the end-of-life comparing oxygen with medical air delivered in identical ways.^{2,3} Additional benefit is questionably demonstrated for people when receiving oxygen. Despite the lack of definitive evidence, consensus guidelines support the use of a therapeutic trial of oxygen in people with breathlessness at the end of life without preliminary blood gas testing.⁴⁻⁶

A well-designed adequately-powered effectiveness study of a real-world palliative care population and true patient-based outcomes is needed to guide clinical practice and funding. In planning such a trial, we surveyed palliative care and respiratory clinicians about their prescription of palliative oxygen. The aim of this survey was to define the duration of a definitive clinical efficacy study on the use of oxygen therapy for breathlessness at the end of life.

Methods: An e-mail survey was sent to all 648 registered palliative care specialists and respiratory physicians in Australia and New Zealand. The questionnaire sought to establish:

- the frequency with which palliative oxygen is prescribed
- the indications for initiating oxygen therapy for someone with a life-limiting illness
- whether further studies were needed to improve clinical practice
- the duration of a therapeutic trial of oxygen for a study to inform real-world clinical practice.

Data were analysed using SPSS. Descriptive statistics were used to summarise respondent characteristics and frequency of response. Relationships between categorical variables were tested using the chi-squared test; two-tailed P values were reported and statistical significance was assumed if $P < 0.05$.

Results: Two-hundred and fourteen clinicians (33%) responded; 93 (63%) palliative care clinicians and 121 (24%) respiratory clinicians. Overall, 58% reported that they believed palliative oxygen was beneficial; 69% of

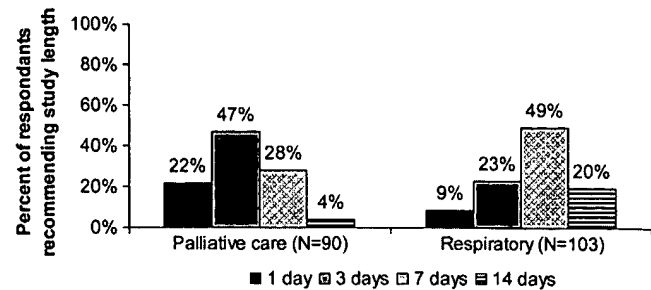


Figure 1 Respondents' recommendation of the length of a definitive clinical trial.

palliative medicine clinicians and 48% of respiratory physicians ($P=0.009$). Palliative medicine clinicians prescribed oxygen frequently (29%) compared with respiratory physicians (9%, $P<0.001$). The most frequently cited reason for prescribing oxygen was 'intractable dyspnoea' (65% overall; 77% of palliative medicine clinicians, 55% of respiratory physicians, $P<0.001$). According to 72% of respiratory physicians responding and 75% of palliative care clinicians, an ideal study to define the benefits and burden of oxygen in the setting of end-of-life care should be between 3 and 7 days of oxygen therapy (Figure 1). Palliative clinicians suggested shorter durations for the study (P for trend <0.001). Quality of life was noted as a key secondary outcome by responding clinicians (23%).

Conclusions: The response rate to the survey was low so the detailed results need to be interpreted with caution. However, the majority of responding clinicians believe palliative oxygen benefits patients. Clinicians commonly prescribe this therapy despite funding mechanisms that limit availability of oxygen in the community.

As a result of this survey, an adequately powered, double-blind multi-site parallel arm randomized controlled trial responding to input from respiratory and palliative clinicians has been initiated in people with dyspnoea at the end of life. Using feedback from the survey, the duration of the study will be 7 days of therapy (oxygen or air). Evidence from this subsequent study should inform day-to-day clinical practice.

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Psychogenic delirium?

Sir – Centeno, Sanz and Bruera in this journal state that ‘in terminally ill cancer patients delirium may be due to organic failure although it may also be due to non-organic factors’.¹ This statement suggests that delirium may be psychogenic which is a viewpoint not consistent with the DSM IV conceptualisation of delirium. The aetiology of delirium is considered by DSM IV to be a direct physiological consequence of a general medical

condition, substance intoxication or withdrawal, use of a medication, toxin exposure or a combination of these factors. Lipowski, a key figure in the evolution of the modern concept of delirium, believed that ‘the presence of one or more organic factors is a necessary condition for delirium to occur’.²

Delirium frequently complicates advanced malignant disease and the dying process. Undoubtedly psychological and cultural influences facilitate, clinically flavour and even precipitate delirium but ‘no single psychological or personality variable has been established as imparting an enduring predisposition to delirium’, let alone cause it.³ Abse opined that ‘hysterics show proneness to delirium’ but offered no supporting data.⁴ It is not evident from the literature that delirium is caused primarily by environmental factors such as an ICU setting.⁵ Whilst psychological interventions are an important component of the management of delirium⁶ this does not imply that psychological factors are deliriogenic.

There are reports in the literature of psychogenic delirium,⁷ psychogenic psychosis,⁸ *bouffees delirantes*⁹ and pseudodelirium.³ These states which are described in adolescents and the elderly do not record cognitive deficits as clinical features. Other primary psychiatric diagnoses are more likely explanations for such case reports. Profoundly anxious persons may appear bewildered but they do not have impairments of consciousness and nor do schizophrenic, manic or dissociative fugue patients. Impairments of consciousness and cognition are recognised to be diagnostic of delirium.

Whilst risking being pedantic, the suggestion that non-organic factors may cause delirium undermines the strenuous efforts in the burgeoning literature stressing the importance of accurate assessment and diagnosis of delirium.

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Patient choice regarding place of death

Sir – To have a choice of where we die is generally accepted to be an integral part of a good death.¹

Surveys show home to be the patients' preferred place of death, with 56 to near 90% wanting to die at home,^{2–4} and only 2% choosing to die in hospital.⁴ Being in hospital during the final illness has been shown to be negatively associated with dying at home.³ This presents a challenge for hospital palliative care teams. Our retrospective data suggested that many people did not achieve their preferred place of death, but reasons for this were hard to define.⁵ Therefore we prospectively surveyed patients referred to a hospital palliative care team to assess our current practice and determine where improvements could be made.

One hundred consecutive patients referred to the Leeds Teaching Hospital Palliative Care Team who were judged clinically to have a prognosis of less than one month or who died unexpectedly were included in the survey. Where death was anticipated (90%) information was collected prospectively.

The mean age was 70 years, 52 were male. Patients had a range of cancer diagnoses and 10% had a non-malignant disease.

The team asked 63% of the patients about their preferred place of death. Of those not specifically asked, 22 were too unwell, ten had died unexpectedly and five were for other reasons. Where preferred place of death was addressed 51% preferred to die at home, 29% in a hospice, 17% in hospital and 3% were unsure.

Of those who expressed a preference, 52% achieved it, with 50% of those wanting to die at home being discharged.

Of the 16 patients who did not get home, two were too unwell to transfer, seven deteriorated unexpectedly, one was receiving active hospital treatment, and five lacked community support.

In those patients with a non-malignant diagnosis six out of ten expressed a preference for place of death. Four were too unwell to discuss this. Four of the six able to express a preference achieved this.

For all patients, median time from admission to hospital and referral to the palliative care team was nine days. Median time from referral to diagnosing dying by the hospital palliative care team was one day, and the median time from referral to death in hospital was five days.

In patients with non-malignant diagnoses, the median time from referral to discharge in those who did achieve their preference was 2 and a half days. In those who did not achieve their preference the median time from referral to death was only one day.

This survey demonstrates that a high percentage of people do achieve their preferred place of death after being in hospital. Fewer than expected wished to die at home, which may reflect a change in preference with declining health. It is a reminder of how complex a decision for patients and families to have to make, with a number of preferences to be balanced at the end of life not just place of care.

Of note is the high number of patients who couldn't discuss their preferred place of death as they were too unwell. This reflects referral patterns to the palliative care service and the confidence of ward teams to recognise when a patient is dying, particularly in patients with non-malignant diagnoses.

Increasing the number of people dying at home may result in financial savings and facilitate choice. Training staff to recognise dying earlier may enable choices to be realised.

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